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Diagnostic Value of Color Doppler Imaging and Pattern Visual Evoked Potential in Primary Open-Angle Glaucoma

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Abstract

Purpose: To evaluate the color Doppler imaging (CDI) and pattern visual evoked potential (P-VEP) examinations in primary open angle glaucoma (POAG) patients and investigate the relation between flow velocities measured by CDI and P-VEP examination in POAG patients.

Methods: Sixty five POAG patients and 45 control subjects underwent CDI evaluation of the ophthalmic artery (OA), short posterior ciliary artery (SPCA) and central retinal arteries (CRA). The peak systolic velocities (PSV) and end-diastolic velocities (EDV) and resistive index (RI) of all retrobulbar vessels were measured. The latency and amplitude of P100 in P-VEP were recorded. The differences of CDI and P-VEP parameters among POAG and control groups were compared. The correlations between CDI parameters, visual field indices and P-VEP in POAG patients were evaluated by Pearson's correlation analysis.

Results: POAG patients had the lower EDV and higher RI in the OA, CRA and SPCA comparing with that of control subjects. Also, POAG patients had lower PSV in OA and CRA comparing with that of control subjects. The latency of P100 in VEP delayed and the amplitude of P100 decreased in the POAG patients comparing with that of the control group. The RI of OA and SPCA were negatively correlated with the mean deviation (MD) values in the POAG patients. The RI of OA was positively correlated with the PSD value in POAG patients. The MD values in POAG patients were negatively correlated with the latency time of P100. The RI of OA was positively correlated with the latency time of P100 and negatively correlated with the amplitude of P100 in the POAG patients.

Conclusions: The combination of the CDI and pattern VEP techniques provides further interpretation of ocular circulatory changes in POAG patients. Further studies are needed for assessment the relationship between circulatory and neural changes.

Keywords: Color doppler imaging; Pattern visual evoked potential; Primary open angle glaucoma

Introduction

Glaucoma is recognized as a leading cause of irreversible blindness in the developed world. It is known that elevated intraocular pressure (IOP) is the primary risk factor for glaucoma [1,2]. Recently, more and more evidences show that vascular deficit also plays an important role in the pathogenesis of glaucomatous optic neuropathy [3,4].

The vascular aetiology of glaucoma hypothesizes that a compromised blood supply to the optic nerve head contributes to optic nerve head damage. Localized damage may occur when ocular perfusion deficits of the optic nerve head, the retina, the choroid or the retrobulbar vessels falls outside the normal range of autoregulation. This may be the result of systemic dysfunction (vasosclerosis, small vessel disease, vasospasms) or a local abnormality in the ocular blood supply which contribute to the nerve fiber loss in glaucomatous optic neuropathy [5-8].

Color Doppler imaging (CDI) has been introduced recently to ophthalmology as a non-invasive imaging method to measure blood flow velocities of retrobulbar vessels. This ultrasound technique uses simultaneous B-scan and Doppler imaging to locate and identify orbital blood vessels: the ophthalmic artery (OA), central retinal artery (CRA) and short posterior ciliary arteries (SPCA). A reduction in flow velocities and an increase in the calculated resistive indices (RI) of all these retro bulbar vessels have been reported in glaucoma patients compared to healthy controls in different studies [9-14]. The blood flow velocities of retro bulbar vessels have been correlated to the visual field defect in glaucoma [15].

Pattern visual evoked potential (P-VEP) is an objective method for checking the visual function and has been shown to be sensitive to glaucomatous neuropathy. Previous studies showed that the P-VEP in glaucoma patients manifested an increased latency and decreased amplitude [16-18] and the P100 latency and amplitude in patients with open angle glaucoma were correlated with the visual field defect [19-21].

The purpose of this study was to compare the differences in CDI and P-VEP examinations between primary open angle glaucoma (POAG) patients and control subjects. In addition, we investigate the relation between flow velocities measured by CDI and P-VEP examinations.

Materials and Methods

Study design

This was prospective comparative study. After explaining the details including the necessity for an examination, we obtained written informed consent from all patients before enrollment. The

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study was approved by Mansoura university hospital trust ethics committee and was carried out in accordance with the Decleration of Helsinki (1989) of the world medical association.

Patients

Sixty five primary open angle glaucoma patients and 45 healthy control subjects meeting the eligibility criteria were included in this prospective clinical study. Each patient chose one eye for study. If the patients with only one eye meeting the eligibility criteria, then the eye was chosen for study. If the patients with two eyes meeting the eligibility criteria, then one eye was chosen at random.

All patients with POAG had glaucomatous optic nerve changes including diffuse or focal neural rim thinning, hemorrhage, enlarged cupping, nerve fiber layer defects with corresponding glaucomatous visual field loss, best-corrected visual acuity more than 0.8, maximum IOP more than 21 mmHg using Goldmann applanation tonometer on a Haag-Streit slit-lamp microscpope and open angle at gonioscopy.

Control subjects were defined as a normal IOP <21 mmHg, normal visual field with standard automated perimetry (SAP), open angle at gonioscopy, normal optic nerve head and retinal nerve fiber layer on clinical examination, best-corrected visual acuity more than 0.8 and a negative family history for glaucoma [22].

Exclusion criteria were included: (1) patients with refractive error more than plus or minus 8 diopters, (2) retinopathy of any type, (3) evidence of intracranial diseases that mimic the disc or field changes were confirmed by plain skull radiography and computed tomography scanning , (4) previous or current use of antiglaucoma medications and previous laser-surgical intervention, (5) patients with exfoliative, pigment dispersion and secondary glaucomas, (6) history of diabetes mellitus, cardiovascular disorders and hypersensitivity to sodium fluorescein.

All subjects' visual fields were assessed by Humphrey field analyzer 750i (Carl Zeiss Meditec, Dublih, CA), program 24-2 full threshold. All patients had the experiences of SAP examination for at least two times respectively and the second SAP visual fields were chosen for the present study. Reliable visual field was defined as having a false-positive error less than 33%, a false-negative error less than 33% and a fixation loss less than 20%. Mean deviation (MD) and pattern standard deviation (PSD) were considered in the study. Visual field defects in SAP was considered significant when 1) two or more contiguous points with a pattern deviation sensitivity loss of $P < 0.01$, or three or more contiguous points with sensitivity loss of $P < 0.05$ in the superior or inferior arcuate areas, or a 10-dB difference across the nasal horizontal midline at two or more adjacent locations and 2) an abnormal result in glaucoma hemifield test [22].

The glaucoma patients were classified as early, moderate and late glaucoma groups based on SAP visual field defects [23]. Early POAG patients ($n = 32$) had early glaucomatous visual field loss defined as MD > -6 dB, moderate POAG patients ($n = 23$) had moderate glaucomatous visual field loss defined as MD from -6 dB to -12 dB, late POAG patients ($n = 10$) had late glaucomatous visual field loss defined as MD > -12 dB.

Methods

All patients had a detailed ophthalmological examination, a color Doppler imaging examination and pattern visual evoked potential (P-VEP). The interval time among the SAP, P-VEP and CDI examinations in the same patient was less than 2 month in order to avoid the effect of the progress of the visual field loss.

CDI examinations (Philips ATL Ultrasound HDI5000, Bothell WA, USA) were performed after a 15 min rest in a thermally controlled room with the patient in the erect and supine positions by the same masked technician. A sterile-coupling gel was applied to the closed eyelids and using a 7.5 mHertz linear-array probe, taking care to avoid any manual pressure on the globe. All flow-velocity waveforms were obtained after angle correction. The ophthalmic artery (OA) was examined approximately 17-20 mm back from the optic nerve head, where it lies parallel and lateral to the optic nerve before giving off its major branches. The nasal and temporal posterior ciliary arteries (NPCA and TPCA) were examined approximately 5–10 mm behind the globe and the results were averaged. The central retinal artery is examined within 5 mm of the retrolaminar portion of the optic nerve. The peak systolic velocity (PSV) and end-diastolic velocity (EDV) in centimeters/ second were obtained from the velocity waves of each artery. The resistive index was calculated using Pourcelot's formula [RI = (PSV - EDV)/PSV] to characterize peripheral vascular resistance of the vessel studied [24].

All the P-VEP examinations (UTAS-E3000, LKC Technologies Inc., Gaithersburg, USA) were performed in an electrically shielded room. Cup-shaped electrodes of silver/silver chloride were placed on identifiable bony landmarks based on a method supported by anatomic studies known as the International 10/20 system [25] on the scalp for recording VEP responses in the following positions: active electrode in Oz (occipital pole), reference electrode in Fz (frontal pole), ground electrode on earlobes. All the patients were seated and wore their optical corrections when necessary. Visual evoked potentials were obtained by instructing the subject to fixate a small red spot in the center of a television screen on which a reversing checkerboard-like stimulus of alternating black and white square was displayed. The luminance of the white areas was 80 cd /m^{-2} with a contrast of at least 75% compared to black squares. The checkerboard pattern reversed at the rate of 2 reversals/second. At the viewing distance of 100 cm the check edges subtended 15 degree of visual angle. The signals were fed into an amplifier with the low frequency cut-off filter set at 1.0 Hertz and the high frequency cut-off filter set at 100 Hertz. The amplitude of P100 is measured from the preceding negative peak N75 to the peak of P100 and the latency is the time from stimulus onset to the peak of each component were considered in the study.

Central corneal thickness (CCT) was measured three times by ultrasonic pachymetry (Sonoscan, model 4000 AP) in all patients on the first visit and the average in each patient was recorded.

Statistical analysis

Data were analyzed using the statistical package SPSS version 15 (SPSS Inc., Chicago, IL, USA). The chi-square test was used to analyze the significance of categorical data. Kolmogorov–Smirnov nonparametric test was used to evaluate the normal distribution of the numerical data. Comparisons between two groups were with student t test for unpaired data using the Bonferroni correction. Correlations of numerical variables were evaluated with Pearson's correlation coefficient. A $P < 0.05$ was considered to be statistically significant.

Results

The general characteristics of the POAG patients and control subjects were summarized in Table 1. There was no significant difference in gender, age, spherical equivalent, diameter of pupil, systolic and diastolic blood pressure among the both groups. The

mean MD, PSD, CCT and IOP in POAG patients were significantly higher than that of control subjects ($P < 0.001$).

The parameters of CDI in 56 POAG patients were out of the normal range. The retrobulbar blood flow velocities and RI of the POAG patients and control subjects were represented in Table 2. POAG patients had the lower EDV and higher RI in the OA, CRA and SPCA comparing with that of control subjects ($P < 0.05$). POAG patients also had the lower PSV in OA and CRA comparing with that of control group ($p < 0.001$).

Parameters	POAG (*n* = 65)	Control (*n* = 45)	*P Value*
Gender (M/F)	33/32	21/24	X2=0.006 P=0.623
Age (years)	58.25 ± 12.21	59.31 ± 14.16	F=0.138 P=0.652
MD (dB)	−7.41 ± 5.35	−0.68 ± 0.65	F=21.123 P=0.002
PSD (dB)	7.20 ± 4.23	1.54 ± 0.53	F=18.411 P=0.012
CCT (µm)	554.57 ± 14.93	542.63 ± 13.12	F=12.451 P=0.003
IOP (mm Hg)	21.16 ± 2.21	16.41 ± 1.22	F=82.625 P=0.001
Spherical equivalent (D)	−2.29 ± 2.12	−1.40 ± 2.05	X2=0.334 P=0.846
Diameter of pupil (mm)	3.33 ± 0.49	3.32 ± 0.41	X2=1.735 P=0.326
Systolic Bl.P (mm Hg)	125.29 ± 7.68	124.36 ± 6.75	F=0.632 P=0.400
Diastolic Bl.P (mm Hg)	75.64 ± 4.53	75.42 ± 5.95	F=0.364 P=0.534

POAG= primary open angle glaucoma, MD= mean deviation, PSD= pattern standard deviation, CCT= central cornea thickness, IOP= intraocular pressure, D= diopter, Bl.P= blood pressure,X2=Chi-square test

Table 1: Characteristics of the studied patients.

Parameters	POAG (*n* = 65)	Control (*n* = 45)	P value
Ophthalmic artery			
PSV	31.86 ± 8.18	38.54 ± 4.24	F=6.332 P=0.003
EDV	8.61 ± 3.22	13.62 ± 3.54	F=12.687 P=0.002
RI	0.84± 0.04	0.65 ± 0.03	F=5.765 P=0.004
Short posterior ciliary artery			
PSV	21.58 ± 5.65	23.81 ± 4.07	F=0.482 P=0.565
EDV	6.73 ± 3.41	7.29 ± 2.04	F=5.648 P=-0.006
RI	0.61 ± 0.04	0.46 ± 0.06	F=3.481 P=0.026
Central retinal artery			
PSV	10.17 ± 2.65	13.27 ± 2.63	F=6.304 P=0.004
EDV	3.40 ± 1.33	4.64 ± 1.65	F=6.335 P=0.004
RI	0.67 ± 0.13	0.45 ± 0.05	F=6.620 P=0.005

Blood flow velocity is given in cm/second, POAG= primary open angle glaucoma, OA= ophthalmic artery, CRA= central retinal artery, SPCA= short posterior ciliary artery, PSV= peak systolic velocity, EDV= end-diastolic velocity, RI= resistive index ,* $P < 0.05$

Table 2: Hemodynamic values measured in the retrobulbar vessels for POAG and control subjects.

Parameters	POAG (*n* = 65)	Control (*n* = 45)	*P Value*
Latency time (ms)	115.14 ± 8.21 (CI:112.72–118.37)	104.12 ± 3.54 (CI:99.18–107.18)	F=13.431 P=0.003
Amplitude (µV)	8.26 ± 3.04 (CI:5.97–8.65)	12.06 ± 5.23 (CI:11.36–12.74)	F=11.414 P=0.004

POAG= primary open angle glaucoma
*$P < 0.05$ versus control

Table 3: Comparisons of the latency time and amplitude of P100 among the POAG patients and control subjects.

Parameters	POAG (*n* = 65)			
	MD (*r* value)	*P*	PSD (*r* value)	*P*
Central retinal artery				
PSV	0.128	0.579	0.007	0.760
EDV	0.230	0.458	-0.232	0.164
RI	0.165	0.331	0.360	0.248
Ophthalmic artery				
PSV	0.323	0.053	-0.240	0.163
EDV	0.015	0.820	-0.053	0.634
RI	-0.434*	0.003	0.413*	0.002
Short posterior ciliary artery				
PSV	0.248	0.164	-0.051	0.656
EDV	0.164	0.251	-0.121	0.323
RI	-0.324*	0.006	0.016	0.527

POAG= primary open angle glaucoma, OA= ophthalmic artery, CRA= central retinal artery, SPCA= short posterior ciliary artery, PSV= peak systolic velocity, EDV= end-diastolic velocity, RI= resistive index
*$P < 0.05$

Table 4: Correlations between the visual field indices and the parameters of hemodynamic values in CDI examination.

	Latency time (*r* value)	*P*	Amplitude (*r* value)	*P*
POAG MD	−0.445*	0.014	0.203	0.247
POAG PSD	0.337	0.063	−0.053	0.612

POAG= Primary open angle glaucoma, MD= mean deviation, PSD= pattern standard deviation

Table 5: Correlations between the visual field indices and the Latency time and amplitude of P100 in POAG patients.

Parameters	POAG (*n* = 65)			
	Latency time (*r* value)	*P*	Amplitude (*r* value)	*P*
Central retinal artery				
PSV	−0.068	0.479	0.210	0.340
EDV	−0.100	0.458	0.232	0.164
RI	0.165	0.331	−0.360	0.248
Ophthalmic artery				
PSV	−0.323	0.053	0.240	0.163
EDV	−0.015	0.820	0.053	0.634
RI	0.354*	0.003	−0.424*	0.015
Short posterior ciliary artery				
PSV	−0.248	0.164	0.051	0.656
EDV	−0.164	0.251	0.121	0.323
RI	0.324	0.053	0.016	0.527

POAG= primary open angle glaucoma, OA= ophthalmic artery, CRA= central retinal artery, SPCA= short posterior ciliary artery, PSV= peak systolic velocity, EDV= end-diastolic velocity, RI= resistive index *$P < 0.05$

Table 6: Correlations between the parameters of P100 in P-VEP and the parameters of hemodynamic values in CDI examination.

The latency time and/or amplitude of P100 in 59 POAG patients were out of the normal range. Table 3 showed the comparisons of the latency time and amplitude of P100 among the POAG patients and control subjects. The latency of P100 in VEP delayed and the amplitude of P100 decreased in the POAG patients comparing with that of control group ($P < 0.001$).

Table 4 showed the correlations between the visual field indices and the parameters of hemodynamic values in CDI examination. The RI of OA was negatively correlated with the MD values in the POAG ($R= -0.434$, $P= 0.003$) patients, the RI of SPCA was also negatively correlated with the MD values in the POAG ($r = -0.324$, $P = 0.006$) patients. The RI of OA was positively correlated with the PSD value in the POAG ($r = 0.413$, $P = 0.002$) patients.

Table 5 showed the correlations between the visual field indices and the latency time and amplitude of P100 in POAG patients. The MD values in the POAG ($r = -0.445$, $P = 0.014$) patients were negatively correlated with the latency time of P100. No significant correlation was found between PSD and latency time, PSD and amplitude of P100 in the POAG patients.

Table 6 showed the correlations between the parameters of P100 in P-VEP and the parameters of hemodynamic values in CDI examination. The RI of OA was positively correlated with the latency time of P100 in POAG ($r = 0.354$, $P = 0.003$) patients. The RI of OA was negatively correlated with the amplitude of P100 in POAG patients ($r = -0.424$, $P = 0.015$).

Discussion

Different devices of ocular blood flow assessment with different limitations are available. Studies need to investigate the relation between blood flow parameters and to assess their potential role in diagnosis of POAG. In addition, the identification of glaucoma patients with abnormal latencies could open the possibility of neuroprotection of unhealthy retinal ganglion cells.

Increased latency and decreased amplitude of P100 in P-VEP had been reported in glaucoma patients [16-21]. Furthermore, the latency of P100 in P-VEP had been used as a marker of reversible ganglion cell damage in trials of neuro-protective agents for the treatment

of glaucoma [26]. P-VEP may reflect the function of retinal ganglion cells (RGCs) objectively and sensitively and the latency of P100 can be used as a measure of early glaucomatous damage before RGCs death. Parisi et al. [16] found that the latency of P100 delayed and amplitude of P100 decreased in primary open angle glaucoma (POAG) patients comparing with that of normal subjects. The present study found that the latency of P100 delayed and amplitude of P100 decreased in POAG patients comparing with that of control subjects, which was consistent with previous investigations [16-21]. Furthermore, we also found the MD values in the POAG patients were negatively correlated with the latency time of P100, which was agreed with the previous studies [18].

Various studies have investigated blood flow velocities and ocular hemodynamics of the retro bulbar vessels in patients with POAG. They revealed that altered retro bulbar circulation is a constant finding and a major factor in the pathogenesis in glaucomatous optic neuropathy [27,28]. Cellini et al. [9] found that the patients with open angle glaucoma had the lower PSV and the higher RI of OA and SPCA comparing with that of normal subjects. Galassi et al. [10] found a significant reduction of PSV in OA in glaucoma patients in comparison with controls. Reduced PSV of these vessels tend to be obvious phenomenon [9-12]. In glaucomatous patients with uncontrolled IOP there was a reduction of EDV and a rise of RI in SPCA and CRA. Trible et al. [14] reported POAG patients had the decreased EDV of OA, CRA and SPCA and the increased RI of these vessels comparing with that of normal subjects. The present study found that POAG patients had the lower EDV and the higher RI in the OA, CRA and SPCA comparing with that of control subjects; POAG patients also had the lower PSV in OA and CRA comparing with that of control subjects which was consistent with Trible et al.'s study [14].

A higher downstream resistance in ocular blood flow may be caused by an elevated IOP, peripheral vasoconstriction particularly at lamina cribrosa, vasosclerosis, or reduced cross section of the vascular bed. All these alternations have been postulated as significant to the pathogenesis of glaucomatous optic neuropathy [29]. Our findings emphasize the downstream resistance of central retinal artery as an important parameter of the circulatory disturbance of the optic nerve head in glaucoma. In addition, the PSV and EDV of the CRA were significantly lower while the RI of CRA was significantly higher in POAG patients revealed that the abnormality of ocular haemodynamic is one important factor of optic nerve damage in POAG.

The present study also found the RI of OA was negatively correlated with the MD values in the POAG patients; the RI of SPCA was negatively correlated with the MD values in the POAG patients; the RI of OA was positively correlated with the PSD value in the POAG patients. These results revealed that the RI of the OA in POAG patients may reliably predict visual field progression.

In the present study, we found that the latency of P100 in POAG patients was positively correlated with RI of OA; the amplitude of P100 in POAG patients was negatively correlated with RI of OA, which suggested that the higher RI of OA revealed more severe visual function damage. Previous study also found that CDI examination may have the predictive value for the visual function damage in glaucoma patients [30].

In conclusion, the results of the present study showed that a significant difference was found in the parameters of CDI and P-VEP between POAG patients and normal control subjects and the certain parameters of CDI were correlated with P-VEP parameters in POAG patients. However, further investigations are needed to demonstrate the relation between flow velocities measured by CDI and multifocal VEP or blue-on-yellow VEP in glaucoma patients.

Declaration of interest

None of the authors has a financial or proprietary in any material or method mentioned. The authors alone are responsible for the content of the paper.

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